Human pluripotent stem cells as a model of trophoblast differentiation in both normal development and disease.

Journal: Proc Natl Acad Sci U S A

Publication Year: 2016

Authors: Mariko Horii, Yingchun Li, Anna K Wakeland, Donald P Pizzo, Katharine K Nelson, Karen Sabatini, Louise Chang Laurent, Ying Liu, Mana M Parast

PubMed link: 27325764

Funding Grants: Molecular Mechanisms of Trophoblast Stem Cell Specification and Self-Renewal, Human pluripotent stem cell-based therapeutics for preeclampsia

Public Summary:
This work establishes a method through which human pluripotent stem cells can be reproducibly differentiated into placental cells. It then provides evidence how these cells can model both normal development of the placenta and the placenta in the setting of a disease, namely Trisomy 21, in which a particular placental cell type is poorly developed. We show that, similar to cells from a Trisomy 21 placenta, human pluripotent stem cells with Trisomy 21 show the same placental cell defect when they are differentiated using our protocol.

Scientific Abstract:
Trophoblast is the primary epithelial cell type in the placenta, a transient organ required for proper fetal growth and development. Different trophoblast subtypes are responsible for gas/nutrient exchange (syncytiotrophoblasts, STBs) and invasion and maternal vascular remodeling (extravillous trophoblasts, EVTs). Studies of early human placental development are severely hampered by the lack of a representative trophoblast stem cell (TSC) model with the capacity for self-renewal and the ability to differentiate into both STBs and EVTs. Primary cytotrophoblasts (CTBs) isolated from early-gestation (6-8 wk) human placentas are bipotential, a phenotype that is lost with increasing gestational age. We have identified a CDX2(+)/p63(+) CTB subpopulation in the early postimplantation human placenta that is significantly reduced later in gestation. We describe a reproducible protocol, using defined medium containing bone morphogenetic protein 4 by which human pluripotent stem cells (hPSCs) can be differentiated into CDX2(+)/p63(+) CTB stem-like cells. These cells can be replated and further differentiated into STB- and EVT-like cells, based on marker expression, hormone secretion, and invasive ability. As in primary CTBs, differentiation of hPSC-derived CTBs in low oxygen leads to reduced human chorionic gonadotropin secretion and STB-associated gene expression, instead promoting differentiation into HLA-G(+) EVTs in an hypoxia-inducible, factor-dependent manner. To validate further the utility of hPSC-derived CTBs, we demonstrated that differentiation of trisomy 21 (T21) hPSCs recapitulates the delayed CTB maturation and blunted STB differentiation seen in T21 placentae. Collectively, our data suggest that hPSCs are a valuable model of human placental development, enabling us to recapitulate processes that result in both normal and diseased pregnancies.